International Journal of Gerontology 17 (2023) 9–12
https://doi.org/10.6890/IJGE.202301_17(1).0002

International Journal of Gerontology

journal homepage: http://www.sgecm.org.tw/ijge/

Original Article

Atrial Fibrillation Known Prior to Stroke and Preceding Oral Anticoagulant Therapy

Ya Ju Lin [a *], Helen Po [a,b]

[a] *Department of Neurology, MacKay Memorial Hospital, Taipei, Taiwan,* [b] *Stroke Center, MacKay Memorial Hospital, Taipei, Taiwan*

ARTICLE INFO

Accepted 29 April 2022

Keywords:
ischemic stroke,
known atrial fibrillation,
non-vitamin K antagonist oral anticoagulant

SUMMARY

Background: Despite anticoagulant therapy, patients with atrial fibrillation are still at high risk of ischemic stroke. This study aimed to determine the effect of known pre-stroke atrial fibrillation on the pre-stroke prescription rate of oral anticoagulants, as well as the factors affecting the prescription.
Methods: This registry-based prospective cohort study included patients with known atrial fibrillation before stroke who were hospitalized between December 1, 2012, to December 31, 2016. We analyzed the use of oral anticoagulants before the onset of index-stroke and stratified patients according to their therapeutic and non-therapeutic anticoagulant status.
Results: Of the 511 acute ischemic stroke patients with atrial fibrillation, 243 (47.6%) were known to have atrial fibrillation before stroke. Only 40 (16.5%) of 243 patients received therapeutic anticoagulation therapy. Patients therapeutic on anticoagulation were more likely to have a lower NIHSS score (7.4 ± 6.6 vs. 10.8 ± 8.4, $p = 0.01$), shorter length of hospital stay (13.1 ± 9.7 vs. 18.8 ± 13.6, $p = 0.01$), and higher rates of good functional outcomes at discharge (40% vs. 25.1%, $p = 0.01$) and at 90 days (60% vs. 39.4%, $p = 0.02$). Lower CHA_2DS_2VASc score (3.5 ± 2 vs. 4 ± 1.5, $p = 0.01$), younger age and male gender were associated with the use of therapeutic anticoagulants before stroke.
Conclusion: In patients with atrial fibrillation, oral anticoagulant therapy after the era of non-vitamin K antagonist oral anticoagulants was still underutilized before the onset of stroke. This underused is associated with increased stroke severity and disability.

1. Introduction

The introduction of non-vitamin K antagonist oral anticoagulant (NOAC) had an enormous impact on the primary and secondary prevention of acute ischemic stroke in the setting of nonvalvular atrial fibrillation (NVAF). However, a large number of patients who were known to have NVAF before the stroke did not receive proper preventive treatment. Compared with strokes in patients without atrial fibrillation (AF), strokes in patients with AF are more often disabling, involve a larger vascular territories, and have a higher mortality rate.[1,2] In addition, patients who underuse NOAC may experience more severe strokes and worse outcomes than patients who use the recommended dose.[3,4] The purpose of this study was to evaluate the rate and determinants of anticoagulant therapy in patients with known AF before stroke and to determine its association with stroke severity and functional outcome since the introduction of NOAC in clinical practice.

2. Methods

This registry-based prospective cohort study retrospectively analyzed patients with acute ischemic stroke with NVAF admitted to our hospital between December 1, 2012, and December 31, 2016. We included patients with: (1) diagnosis of NVAF known prior to the index event; (2) available information about anticoagulation therapy prior to and after stroke onset; and (3) follow up for at least 3 months or longer after the index event for the functional outcome. The following patients were excluded: (1) missing information on antithrombotic treatment before the index event; and (2) lost to follow up (Figure 1).

The following clinical data were collected: age, gender, body weight, smoking, creatinine clearance (calculated using the Cockcroft-Gault equation),[5] type of AF (paroxysmal or sustained), vascular risk factors (hypertension, diabetes mellitus, and dyslipidemia), and past medical history (stroke, congestive heart failure, and coronary heart disease). The CHA_2DS_2-VASc score was calculated for each patient as previously described[6] with the index stroke not counted as "history of ischemic stroke". Stroke severity on admission was assessed using the NIHSS score.[7] Severe stroke was defined as NIHSS ≥ 11 points.[8] All patients had a non-contrast computed tomography (CT) on admission and underwent further in-hospital magnetic resonance imaging (MRI). In addition, all patients had 12-lead electrocardiogram and 24 hours Holter monitoring. The cardiologists confirm the diagnosis of AF. Transthoracic echocardiography was used to measure the diameter of left atrium in all patients.

We recorded the anticoagulation treatment before the stroke and after the index event. Preceding antithrombotic treatment was determined and defined as receiving antithrombotic treatment within 7 days before the index event. For the purpose of this study, we divided patients into 2 groups according to antithrombotic medication prescribed before the index event: therapeutic (standard

* Corresponding author. Department of Neurology, MacKay Memorial Hospital, Taipei, Taiwan.
E-mail address: yjl.5824@mmh.org.tw (Y. J. Lin)

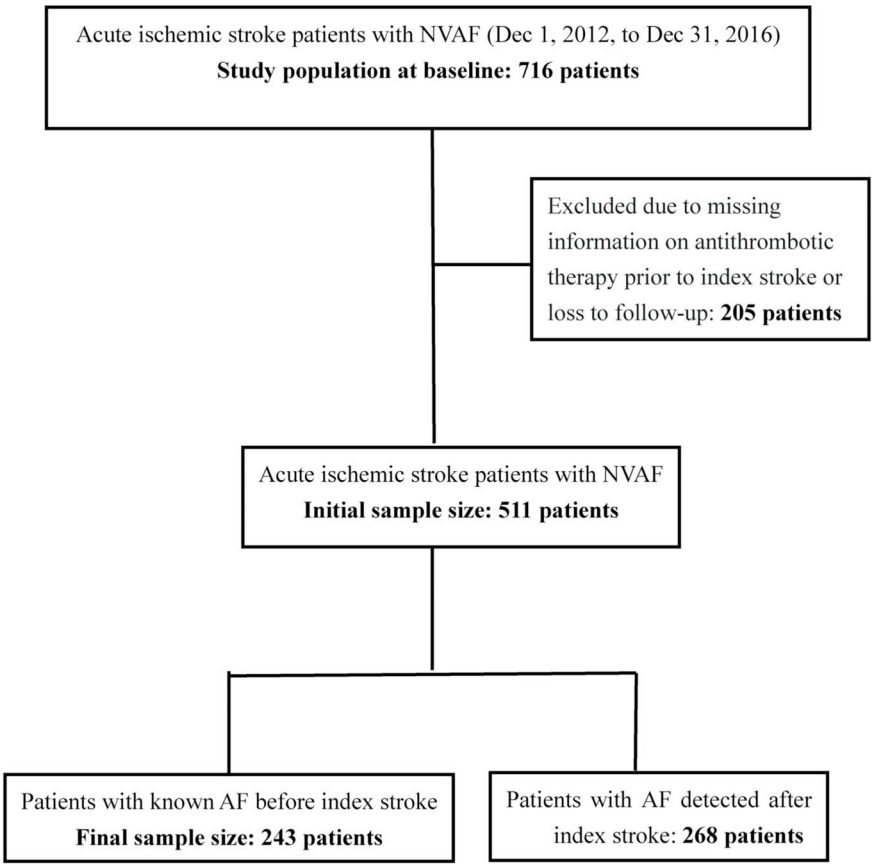

Figure 1. Flowchart of the study population showing inclusion and exclusion criteria. NVAF, non-valvular atrial fibrillation.

dose of NOAC) and non-therapeutic (underdose of NOAC, only antiplatelet and no antithrombotic). The prescription dose of NOAC was evaluated based on the manufacturer's labeling recommendations in Taiwan. The criteria for the standard doses of different NOAC differ according to age, body weight, renal function, and concomitant medications. Underdose of NOAC is defined as the use of off-label doses in patients who do not meet the dose reduction criteria. Patients treated with antiplatelet agents with a CHA_2DS_2-VASc score of ≥ 2 were considered inadequately treated according to the current guidelines.[9] We also collected data on oral anticoagulant prescriptions after the index stroke and at hospital discharge. However, reasons why anticoagulant therapy was not prescribed before and after the stroke were not obtained in this study. We recorded the length of hospital stay for the index stroke. Functional outcomes at hospital discharge and 90 days after admission were evaluated using the modified Rankin Scale (mRS).[10] Patients with an mRS score of 0 to 2 were classified as having a good functional outcome, while those with an mRS score > 2 were classified as having a poor functional outcome. This study was approved by the Institutional Review Board of MacKay Memorial Hospital, and the requirement for informed consent was waived.

Statistical analyses were performed using a commercially available software package (IBM SPSS version 26.0). We used independent-sample t-tests for continuous variables and chi-square or Fisher's exact tests for categorical variables to compare the clinical characteristics between the two groups. Using a binary logistic regression model, we determined the factors associated with the severe stroke on admission, and poor functional outcome at discharge and 90 days after admission. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. All reported p-values are based on a two-tailed test, and $p < 0.05$ is considered statistically significant.

3. Results

Among 511 patients with NVAF who experienced an acute ischemic stroke, 243 (47.6%) had a medical history of AF before the index stroke while 268 (52.4%) had no history of AF, and AF was detected after the index ischemic stroke (Figure 1). Of 243 patients who had a history of AF (mean age, 76.6 ± 11.1 years; 53% women), 203 (83.5%) were not receiving therapeutic anticoagulation prior to stroke, and 40 (16.5%) were receiving therapeutic anticoagulation. Table 1 describes the baseline characteristics of 243 patients with known AF before the index stroke. There was a significant difference in mean age between the two groups classified based on prior antithrombotic drug use ($p = 0.017$; Table 1). The mean age of patients in the non-therapeutic group (77.3 ± 10.6 years) was higher than that in the therapeutic group (72.8 ± 12.9 years). Patients receiving therapeutic anticoagulation were less likely to be female and had lower pre-stroke CHA_2DS_2-VASc score (3.5 ± 2 vs. 4 ± 1.5, $p = 0.010$). The proportions of patients with hypertension, diabetes, dyslipidemia, congestive heart failure, coronary artery disease, previous stroke or TIA, and smoking did not differ significantly between the two groups. In addition, no other significant differences were found in the type of AF and left atrial size.

The severity of the neurological deficits on admission (NIHSS score), the length of hospital stay, and the mRS score at discharge and 90 days after admission are presented in Table 2. Initial stroke severity and length of hospital stay varied with antithrombotic therapy prior to index stroke. Patients receiving non-therapeutic anticoagulation had a significantly higher NIHSS score on admission (10.8 ± 8.4 vs. 7.4 ± 6.6, $p = 0.018$) and longer duration of hospital stay (18.8 ± 13.6 vs. 13.1 ± 9.7, $p = 0.012$). We also observed significant differences in good functional outcomes at discharge ($p =$

Table 1
Baseline characteristics of 243 patients with known AF before the index stroke based on prior antithrombotic drug use.

	Therapeutic	Non-therapeutic	*p*-value
No. of patients	40	203	
Age, yr (mean ± SD)	72.8 ± 12.9	77.3 ± 10.6	0.017
Female sex, n (%)	13 (32.5%)	115 (56.7%)	0.006
Risk factors, n (%)			
Hypertension	32 (80%)	173 (85.2%)	0.474
Diabetes	10 (25%)	61 (30%)	0.574
Dyslipidemia	25 (62.5%)	127 (62.6%)	1.0
Congestive heart failure	1 (2.5%)	10 (4.9%)	0.697
Coronary heart disease	10 (25%)	76 (37.4%)	0.151
Prior stroke or TIA	13 (32.5%)	65 (32%)	1.0
Smoking	11 (27.5%)	35 (17.2%)	0.183
Atrial fibrillation type (sustained versus paroxysmal)	38:2	188:15	0.714
Left atrial size (millimeters, mean ± SD)	38.7 ± 6.8	38.5 ± 6.8	0.813
CHA_2DS_2-VASc score (mean ± SD)	3.5 ± 2	4 ± 1.5	0.010

Table 2
Stroke severity and functional outcomes of 243 patients with known AF according to prior antithrombotic drug use.

	Therapeutic	Non-therapeutic	*p*-value
No. of patients	40	203	
NIHSS score (mean ± SD)	7.4 ± 6.6	10.8 ± 8.4	0.018
Length of hospital stay (days)	13.1 ± 9.7	18.8 ± 13.6	0.012
mRS score of 0–2 at discharge, n (%)	16 (40%)	51 (25.1%)	0.011
mRS score of 0–2 at 90 days, n (%)	24 (60%)	80 (39.4%)	0.022

mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale.

0.011) and 90 days after admission (p = 0.022). Table 3 shows the associations of therapeutic anticoagulation and male gender with the severe stroke at admission and poor functional outcome at discharge and 90 days after admission using binary logistic regression models. Patients who did not receive therapeutic anticoagulation had significantly worse functional outcomes after 90 days of admission than those who received therapeutic anticoagulation. However, this trend was not observed in poor functional outcomes at discharge in the therapeutic group.

4. Discussion

Non-vitamin K antagonist oral anticoagulant have been increasingly used as an alternative to warfarin for the prevention of ischemic stroke in patients with NVAF.[11] Despite its proven efficacy and numerous international guideline recommendations, many patients fail to receive proper treatment for stroke prevention.[12,13]

The main finding of this study was that, despite specific indications, therapeutic anticoagulation was significantly underused (16.5% [40/243]) in patients with known AF prior to stroke. This finding highlights the inadequacy of current primary and secondary stroke prevention in patients with NVAF and provides further evidence for subsequent complications. Previous studies of oral anticoagulant (OAC) use in AF patients with prior ischemic stroke have reported OAC use in 15.7% to 29.8%. After the emergence of NOAC, the use of OAC increased from 22.2% in 2013 to 40.6% in 2018.[14–17] Several other studies have reported increased use of NOAC in patients with AF.[18,19] This finding can be attributed to the stable pharmacokinetic profiles and no need for blood monitoring as well as the efficacy and safety of NOAC.[20] The high proportion of patients not receiving appropriate treatment observed in our study may be due to bias in patient selection, as a stroke is often the result of inappropriate treatment.

Consistent with previous findings,[16,17,21–24] our study showed that prior therapeutic anticoagulation in patients with known AF was associated with a significantly lower stroke severity at the time of admission. As shown, the NIHSS score at admission had a significant impact on the mRS score at discharge and 90 days after admission. Therapeutic anticoagulation before stroke was associated with higher odds of good functional outcomes compared with patients who did not receive therapeutic anticoagulation.

In contrast to previous studies,[4,25] our study reported that patients with higher pre-stroke CHA_2DS_2-VASc scores did not receive therapeutic anticoagulation. This data reflects the reluctance of physicians to prescribe adequate oral anticoagulants due to excessive fear of bleeding events rather than ischemic events.

In line with previous studies,[4,17,26,27] our study confirms that younger age and male gender were factors associated with therapeutic anticoagulation use prior to the index stroke in patients with known AF.

Although the use of standard doses of NOAC is as effective as warfarin in Asian patients, lower doses of NOAC are more commonly used in actual clinical practice in Asia.[28] Asian patients had a higher absolute risk of ischemic stroke using low-dose NOAC than non-Asian patients.[29,30] Considering the dose-dependent efficacy of NOAC, appropriate dose measurements should be performed in clinical practice.

We speculate that there are several reasons for the underuse of therapeutic anticoagulation in our study. Advanced age and concomitant diseases associated with bleeding risk may be important

Table 3
Odds ratios and 95% confidence intervals for antithrombotic therapy before stroke with regard to severe stroke (NIHSS ≥ 11) on admission and poor functional outcome (mRS > 2) at discharge and 90 days after admission.

	NIHSS ≥ 11 on admission		mRS > 2 at discharge		mRS > 2 at 90 days	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Non-therapeutic	1 [reference]		1 [reference]		1 [reference]	
Therapeutic	0.419 (0.194–0.902)	0.026	0.503 (0.248–1.501)	0.057	0.491 (0.247–0.975)	0.042
Male gender	0.394 (0.232–0.670)	0.001	0.386 (0.216–0.692)	0.001	0.362 (0.214–0.612)	0.001

factors in determining antithrombotic therapy in clinical practice. Another factor most associated with non-prescription of OAC was previous use of antiplatelet agents. This could lead to physician preferring the use of antiplatelet agents rather than OAC in patients with AF.

Our study has several limitations. First, this is a single-center retrospective analysis, and the findings of this study may not be generalizable. Hence, these findings must be validated in large multicenter studies. Second, although the data were collected prospectively, the statistical analysis was retrospective and thus prone to bias. Third, this study included only NVAF patients who had an acute ischemic stroke. Patients with NVAF treated with different antithrombotic regimens who did not have an acute ischemic stroke were not included in this study. Therefore, we were unable to draw conclusions about the quality of stroke prevention in patients with NVAF in the general population. Fourth, due to lack of routine anticoagulation monitoring of NOAC therapy, it is not possible to estimate medication adherence to NOAC therapy before stroke. Fifth, information on pre-stroke antithrombotic therapy is missing for some patients. These patients were excluded from this study, which may have biased this analysis. Sixth, reasons for not using antithrombotic therapy were not documented. The absence of documented reasons for non-use does not mean that there are no legitimate reasons for non-use. Undocumented factors (such as previous bleeding or insufficient patient adherence) influencing the physician choice of treating individual patients with therapeutic anticoagulation before stroke might be partly affecting the results of our study.

In conclusion, our study demonstrates that, despite the introduction of NOAC in clinical practice, physician preference for OAC treatment in high-risk NVAF patients has not improved in recent years. Therapeutic anticoagulation prior to stroke significantly reduced stroke severity on admission and improved functional outcomes at discharge and 90 days after admission.

Conflicts of interest

None.

References

1. Marini C, De Santis F, Sacco S, et al. Contribution of atrial fibrillation to incidence andoutcome of ischemic stroke: results from a population-based study. *Stroke*. 2005;36:1115–1119.
2. McGrath ER, Kapral MK, Fang J, et al. Association of atrial fibrillation with mortality and disability after ischemic stroke. *Neurology.* 2013;81:825–832.
3. Kato Y, Hayashi T, Tanahashi N, et al. The dose of direct oral anticoagulants and stroke severity in patients with acute ischemic stroke and nonvalvular atrial fibrillation. *J Stroke Cerebrovasc Dis*. 2018;27:1490–1496.
4. Jung YH, Choi HY, Lee KY, et al. Stroke severity in patients on non-vitamin K antagonist oral anticoagulants with a standard or insufficient dose. *Thromb Haemost.* 2018;118:2145–2151.
5. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31–41.
6. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. *Chest.* 2010;137:263–272.
7. Lyden P, Brott T, Tilley B, et al. Improved reliability of the NIH Stroke Scale using video training. NINDS TPA Stroke Study Group. *Stroke.* 1994;25:2220–2226.
8. Haeusler KG, Konieczny M, Endres M, et al. Impact of anticoagulation before stroke on stroke severity and long-term survival. *Int J Stroke.* 2012;7:544–550.
9. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J AM Coll Cardiol.* 2014;64:e1–e76.
10. Bonita R, Beaglehole R. Recovery of motor function after stroke. *Stroke.* 1988;19:1497–1500.
11. Olesen JB, Sørensen R, Hansen ML, et al. Non-vitamin K antagonist oral anticoagulation agents in anticoagulant naïve atrial fibrillation patients: Danish nationwide descriptive data 2011–2013. *Europace.* 2015;17:187–193.
12. Wehbe RM, Yadlapati A. Underuse of oral anticoagulants for nonvalvular atrial fibrillation: past, present, and future. *Tex Heart Inst J.* 2016;43:287–290.
13. Giustozzi M, Agnelli G, Quattrocchi S, et al. Rates and determinants for the use of anticoagulation treatment before stroke in patients with known atrial fibrillation. *Cerebrovasc Dis Extra.* 2020;10:44–49.
14. Kim BJ, Kim HJ, Do Y, et al. The impact of prior antithrombotic status on cerebral infarction in patients with atrial fibrillation. *J Stroke Cerebrovasc Dis.* 2014;23:2054–2059.
15. Sakamoto Y, Okubo S, Sekine T, et al. Prior direct oral anticoagulant therapy is related to small infarct volume and no major artery occlusion in patients with stroke and non-valvular atrial fibrillation. *J Am Heart Assoc.* 2018;7:e009507.
16. Xian Y, O'Brien EC, Liang L, et al. Association of preceding antithrombotic treatment with acute ischemic stroke severity and in-hospital outcomes among patients with atrial fibrillation. *JAMA.* 2017;317:1057–1067.
17. Yi X, Lin J, Han Z, et al. Preceding antithrombotic treatment is associated with acute ischemic stroke severity and functional outcome at 90 days among patients with atrial fibrillation. *J Stroke Cerebrovasc Dis.* 2019;28:2003–2010.
18. Huisman MV, Rothman KJ, Paquette M, et al. The changing landscape for stroke prevention in AF: findings from the GLORIA-AF registry phase 2. *J Am Coll Cardiol.* 2017;69:777–785.
19. Zimny M, Blum S, Ammann P, et al. Uptake of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation – a prospective cohort study. *Swiss Med Wkly.* 2017;147:w14410.
20. Eikelboom JW, Quinlan DJ, Hirsh J, et al. Laboratory monitoring of non-vitamin K antagonist oral anticoagulant use in patients with atrial fibrillation: a review. *JAMA Cardiol.* 2017;2:566–574.
21. O'Donnell M, Oczkowski W, Fang J, et al. Preadmission antithrombotic treatment and stroke severity in patients with atrial fibrillation and acute ischaemic stroke: an observational study. *Lancet Neurol.* 2006;5:749–754.
22. Audebert HJ, Schenk B, Schenkel J, et al. Impact of prestroke oral anticoagulation on severity and outcome of ischemic and hemorrhagic stroke in patients with atrial fibrillation. *Cerebrovasc Dis.* 2010;29:476–483.
23. Hellwig S, Grittner U, Audebert H, et al. Non-vitamin K-dependent oral anticoagulants have a positive impact on ischaemic stroke severity in patients with atrial fibrillation. *Europace.* 2018;20:569–574.
24. Meinel TR, Branca M, De Marchis GM, et al. Prior anticoagulation in patients with ischemic stroke and atrial fibrillation. *Ann Neurol.* 2021;89:42–53.
25. Jung YH, Kim YD, Kim J, et al. Initial stroke severity in patients with atrial fibrillation according to antithrombotic therapy before ischemic stroke. *Stroke.* 2020;51:2733–2741.
26. Gundlund A, Xian Y, Peterson ED, et al. Prestroke and poststroke antithrombotic therapy in patients with atrial fibrillation results from a nationwide cohort. *JAMA Netw Open.* 2018;1:e180171.
27. Hellwig S, Grittner U, Herm J, et al. Temporal trends in pharmacological stroke prevention in patients with acute ischemic stroke and known atrial fibrillation. *J Stroke Cerebrovasc Dis.* 2020;29:105266.
28. Chan YH, Yen KC, See LC, et al. Cardiovascular, bleeding, and mortality risks of dabigatran in Asians with nonvalvular atrial fibrillation. *Stroke.* 2016;47:441–449.
29. Wang KL, Giugliano RP, Goto S, et al. Standard dose versus low dose non-vitamin K antagonist oral anticoagulants in Asian patients with atrial fibrillation: a meta-analysis of contemporary randomized controlled trials. *Heart Rhythm.* 2016;13:2340–2347.
30. Wang KL, Lip GY, Lin SJ, et al. Non-vitamin K antagonist oral anticoagulants for stroke prevention in Asian patients with nonvalvular atrial fibrillation: meta-analysis. *Stroke.* 2015;46:2555–2561.